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Original article

Daily life stress reactivity in remitted versus non-remitted depressed individuals

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ABSTRACT

Background: Little is known about how daily life mood reactivity to minor stressors (stress reactivity) might change following major depressive disorder (MDD) treatment. We investigate whether (i) mood states and appraisals of daily stressors change after treatment; (ii) stress reactivity to event, activity, or social stress differs; (iii) stress reactivity depends on severity of residual depressive symptoms; and (iv) stress reactivity in individuals with remitted or non-remitted depression differ from that of never-depressed individuals.
Methods: Thirty depressed individuals participated in an experience sampling study before and after a treatment period of 18 months; 39 healthy individuals formed a comparison group. Reactivity of positive affect (PA) and negative affect (NA) to daily stressors were measured.
Results: More residual symptoms were associated with larger NA responses to stress. Compared to healthy controls, participants with non-remitted MDD showed higher NA-reactivity to all stressors. In contrast, stress reactivity to event and activity stressors was normalized in remitted patients. However, they still showed heightened NA-reactivity to social stress.
Conclusions: Greater stress reactivity to event and activity stress appears to be state-dependent. The heightened social stress reactivity in remitted patients suggests that sensitivity to social stress may reflect an underlying vulnerability in MDD.

1. Introduction

Major depressive disorder (MDD) is characterized by persistent low mood and loss of interest or pleasure in normally enjoyable activities, reflected in high levels of negative affect (NA) and low levels of positive affect (PA) [12]. MDD is further characterized by high rates of relapse and recurrence [7,17], even in patients receiving treatment [38].

Alterations in mood reactivity to stressors (stress reactivity) in MDD have been examined by two broad methodological strategies. First, most studies that examined mood responses to experimental stressors reported blunted reactivity to negative (and positive) events, giving support for the Emotion Context Insensitivity (ECI) theory [9,36]. A second approach consists of examining mood reactivity to minor stressors in daily life with the use of ecological momentary assessment techniques like the experience sampling method (ESM) [16,14]. Until now, ESM studies have focused on stress reactivity to three different types of stressors; *event* stress (stress reactivity following small events), *activity* stress (reactivity while appraising current activities), and *social* stress (reactivity associated with the appraisal of current interpersonal context). First, some studies examined mood alterations following small negative events [10,32,41]. Peeters et al. (2003) reported blunted stress responses (i.e., smaller increases in NA and smaller decreases in PA) following negative events in depressed participants compared to a healthy comparison group. In contrast, Bylsma et al. (2011) and Thompson et al. (2012) found no differences between depressed and healthy participants in either PA or NA-reactivity to negative events. Two other studies investigated stress reactivity to activity-related stress, operationalized as unfavorable appraisals of the current activity [44,31]. Using data from the sample described by Peeters et al.

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(2003), Myin-Germeys et al. (2003) found increased NA-reactivity to activity stress in depressed participants, compared to healthy controls. A similar pattern was found in a comparison of depressed participants that were about to participate in an imipramine treatment and healthy controls [44]. Finally, stress reactivity has been investigated in relation to social stress. This is relevant for MDD, as much research has shown that social stress puts people at risk for the development or recurrence of MDD [4,13,43,42]. A body of literature also supports the notion that depressed individuals often experience being in social situations as highly stressful [20,23], resulting in feelings of entrapment and the wish to escape [19]. In the ESM study by Myin-Germeys et al. (2003) mentioned above, social stress in daily life was assessed by asking participants to what extent they would rather be alone than in the present company. The desire to be alone was associated with larger increases in NA in depressed compared to healthy participants, interpreted as increased reactivity to social stress in MDD.

However, little is known about changes in daily life stress reactivity following treatment. Insight into differences in daily life stress reactivity among individuals with remitted versus non-remitted MDD, as compared to healthy, never-depressed individuals, may help elucidate the mechanism through which daily stress is linked to episodes of MDD, remission, and risk for recurrence. Next, it remains unclear whether clinical improvement is accompanied by normalization of daily stress reactivity. To our knowledge, only one study in MDD has examined post-treatment changes in mood reactivity to daily stress. Sixty-three depressed patients took part in an ESM study prior to and again after six weeks of treatment with imipramine or placebo [44]. NA-reactivity to daily stressors at baseline decreased after six weeks in both the placebo and the imipramine arm, with more pronounced changes in the active treatment group. However, it is not known whether this change in NA-reactivity would be sustained over a longer period of treatment, or following remission. Finally, we do not know whether mood reactivity to stressors in depressed individuals who do not profit from treatment and thus develop a more chronic condition differs from that of individuals with remitted MDD. This is clinically relevant, as a myriad of studies have shown that treatment efficacy decreases when MDD becomes more chronic [15]. A prolonged episode of MDD might hypothetically influence stress reactivity in ways that make depressed individuals more resistant to therapeutic interventions.

Aims of the study:

- do momentary mood states, negative event frequencies, and appraisals of stress, current activities, and social company change after standard MDD treatment?
- does post-treatment stress reactivity differ according to the type of daily stressor (event, activity, or social stress)?
- does stress reactivity differ in relation to the severity of residual depressive symptoms after treatment?
- does stress reactivity in individuals with remitted or non-remitted depression differ from that of healthy, never-depressed individuals in daily life?

2. Methods

This study is a follow-up extension of an earlier study by Peeters et al. [32]. In this study, mood reactivity to small events in daily life was examined in clinically depressed participants with the use of ESM prior to treatment. Mood reactivity of depressed participants was compared with those of healthy controls. For details about participants and treatment procedure, see [32] and [33], respectively.

2.1. Participants

Forty-six participants fulfilling Diagnostic and Statistical Manual of Mental Disorders (4th ed., DSM–IV)[3] criteria for MDD as their primary diagnosis, as assessed with the Structured Clinical Interview for DSM-IV (SCID; [18] by a research psychiatrist (FP)). Participants were recruited among subjects seeking treatment at a university-affiliated mental health centre or the outpatient department of a psychiatric hospital in Maastricht, the Netherlands. Exclusion criteria were current substance abuse or psychotic symptoms (both assessed with the SCID) and insufficient fluency in Dutch. None of the participants was using antidepressants during the pre-treatment (baseline) measurement, but use of low-dose anxiolytic drugs was allowed. Thirty-nine healthy participants, matched as a group to the patient sample for gender and age, were recruited from available research pools, through staff from academic affiliations, and an advertisement in a local newspaper. Additional exclusion criteria for the healthy participants were a lifetime history of any DSM-IV[3] Axis I disorder (assessed with the initial screening section of the SCID) [18] or any inpatient treatment for an Axis I disorder in a first-degree relative.

Depressed and control participants took part in an experience sampling (ESM) procedure for six days at baseline. Immediately thereafter, all depressed participants entered a naturalistic treatment phase that consisted of pharmacotherapy and supportive psychotherapy, according to current practice guidelines. After 18 months, 30 of the initial 46 depressed participants agreed to take part in a second ESM period. Clinical outcome at 18 months was measured with the Hamilton Depression Rating Scale (HDRS; [22], with remission defined as an HDRS score ≤ 7 [46]). Control participants didn't take part in this second ESM assessment. Participants in the follow-up study did not significantly differ from non-participants with respect to gender (female) (56.6% vs 60%; $z = 0.213$, $P = 0.831$), symptom severity (HDRS score) (24.2 vs 23.6; $t(43) = -0.426$, $P = 0.672$), benzodiazepine use (10% vs 0%; $z = -1.31$, $P = 0.191$), previous episodes (50% vs 20%; $z = 1.936$, $P = 0.053$) or positive family history (56.6% vs 53.3%; $z = 0.212$, $P = 0.832$), as assessed at baseline. The study was approved by the local medical ethics committee, and written informed consent was obtained from all participants. Participants were paid $30 for completing the study.

2.2. Experience sampling method

The ESM was used to collect data from participants at selected moments during their daily activities. Participants received a digital wristwatch and a set of ESM self-assessment forms collated in a booklet for each day. The wristwatch was programmed to emit a signal ("beep") at an unpredictable moment in each of ten 90-minute time blocks between 7:30 and 22:30, on six consecutive days, resulting in a maximum of 60 beeps per person. After each beep, participants filled out an ESM self-assessment form, including ratings of current mood and context. Participants were instructed to complete their reports immediately after the beep, thus minimizing memory distortion, and to record the time at which they completed the form. Reports not completed within 25 min after the actual beep were considered invalid. Participants with fewer than 20 valid reports were excluded from the analysis. All follow-up participants met our inclusion criteria of submitting at least 20 valid reports.

At baseline, participants completed an average of 85% of all possible responses within the time limit, resulting in an average number of valid responses of 50.7 per participant. Mean time between prompt and response (in minutes) was lower in the healthy (M = 4.67, SD = 2.12), than in the depressed group at

baseline (M = 6.52, SD = 3.54), $t(83) = 2.86$, $P = 0.005$. Mean number of valid responses was higher in the healthy (M = 53.1, SD = 4.87) than in the depressed group (M = 48.6, SD = 7.49), $t(83) = 3.23$, $P = 0.002$. Mean number of valid social stress responses was 70% of the maximum possible responses within the time limit. Mean number of valid social stress responses in the healthy group (M = 39.7, SD = 11.1) was similar to depressed group (M = 33.8, SD = 14.8), $t(83) = 1.18$, $P = 0.239$.

At follow-up, participants completed an average of 81% of all possible responses within the time limit. Mean number of valid responses in the remitted group (M = 50.9, SD = 7.98) was similar to the non-remitted group (M = 47.2, SD = 8.53), $t(28) = -1.17$, $P = 0.252$. Mean time between prompt and response (in minutes) in the remitted group (M = 6.16, SD = 4.08) was also similar to the non-remitted group (M = 6.72, SD = 3.16), $t(28) = 0.41$, $P = 0.681$.

At follow-up, mean number of valid social stress response was 58% of all possible responses within the time limit. Mean number of valid social stress responses in the remitted group (M = 39.4, SD = 12.55) was similar to the non-remitted group (M = 32.1, SD = 11.89), $t(28) = -1.59$, $P = 0.123$.

2.3. Measures of momentary mood

Mood states were assessed at each beep with 20 adjectives rated on 7-point scales (1 "not at all" to 7 "very"). Principal components analyses of baseline data, with varimax rotation on mean scores aggregated per person and on within-person z-scores, identified two factors with Eigen values greater than 1. These factors accounted for 81% of the total between-person variance in mean mood levels and 46% of the within-person variance in mood states. Ratings on the items anxious, irritated, restless, tense, guilty, edgy, distractible, and agitated were averaged to form a negative affect (NA) scale (Cronbach's $\alpha = 0.95$). Ratings on the items energetic, enthusiastic, happy, cheerful, talkative, strong, satisfied, and self-assured were averaged to form a positive affect (PA) scale (Cronbach's $\alpha = 0.97$). The items gloomy, lonely, tired, and calm had similar loadings on each of the two factors and were therefore excluded from the NA and PA scales.

2.4. Measures of stress

2.4.1. Daily life stress was measured in three different ways

2.4.1.1. Event stress. After each beep, subjects responded to the question "Did you experience a negative event or situation since the previous beep?". Participants who answered affirmatively were asked briefly to describe the event in their ESM booklet and to rate the event on three appraisal dimensions: stressfulness, unpleasantness, and importance (single items, from 1 "not at all" to 7 "very much"). For the current paper, event stress was defined as the occurrence of a negative event in the preceding interval, scored 1 (yes) or 0 (no). Although participants were instructed to report only external events or situations that actually took place in their daily environment in the preceding interval, some event reports clearly referred to internal states (e.g., current ruminations about past events, personal health concerns). Following pre-established criteria, the research team identified such internal events by consensus and omitted them from subsequent analyses, to avoid confounding of event and mood measures.

2.4.1.2. Activity stress. After each beep, participants rated three aspects of their current activity (from 1 "not at all" to 7 "very much"). The activity stress score was calculated as the mean rating for the items "I am not skilled at this activity", "This activity requires effort", and "I enjoy this activity" (reverse-coded so that high scores reflect lack of enjoyment) (Cronbach's $\alpha = 0.83$).

2.4.1.3. Social stress. Social stress was operationalized as the extent to which an individual would rather be alone than in the present company. If participants indicated being with others at the moment of the beep, they were then asked to rate how much they would have preferred to be alone on a 7-point scale ranging from 1 "not at all" to 7 "very much". The intraclass correlation coefficient (ICC) of social stress on the subject level is 0.96 and at the beep level 0.85.

2.5. Statistical approach

To examine pre- to post-treatment changes in stress and mood states in the initially depressed but non-remitted participants at follow-up, we used paired *t*-tests to compare individuals' event frequencies and mean ratings for event stress, activity stress, social stress, PA and NA at follow-up versus baseline. We next compared these measures between remitted participants at follow-up and healthy controls with a two sample unpaired *t*-test.

Because ESM data have a hierarchical structure, with multiple observations (level 1) clustered within days (level 2) within subjects (level 3), further analyses were performed with multilevel regression modelling, which takes the variability associated with each level into account [40]. The dependent variable was either NA or PA. The Stata v.12.1 procedure XTMIXED [26] was used to estimate fixed effects, with random intercepts, random slopes, and an unstructured covariance matrix applied, in order to avoid inference bias that could inflate the type I error rate. For significant interactions (non-remitted versus healthy controls and remitted versus healthy controls), stratified analyses were conducted to clarify group differences. Further, effect sizes of the interactions between the groups and appraised social stress were calculated by applying and testing the appropriate linear combinations using the STATA LINCOM command. These effect sizes were used to graphically illustrate group differences at each level of social stress (from "not at all" until "very much"). Standard errors were calculated for each level of social stress and were depicted in the figure with error bars.

A significance level of $P < 0.05$ was used (two-sided tests). In order to use negative events as a predictor in the model, they were dummy-coded (0 or 1). The event appraisal scores were centered around the grand mean or were set to zero if no event was reported, so that inclusion in the model would not automatically change the previously estimated effects of events on mood.

We examined stress reactivity at 18-month follow-up by estimating (in separate models) the effects of event stress, activity stress, and social stress on NA and PA. Further, by testing interactions between each of the three types of stress and the HDRS score, we investigated whether changes in daily life stress reactivity were related to the severity of residual depressive symptoms post-treatment. Last, we compared stress reactivity to negative events, activity stress, and social stress in remitted and non-remitted patient groups with that in the healthy comparison group. To do this, we estimated multilevel models with mood state as outcome and, as predictors, group, stress (event, activity, or social), and the group by stress interaction.

3. Results

3.1. Clinical characteristics of the MDD sample at follow-up

Among the 30 depressed participants (of whom 17 women), mean HDRS score was significantly lower at post-treatment follow-up (M = 10.8, SD = 7.8) compared to baseline (M = 24.2, SD = 4.1), $t(29) = 8.2$, $P < 0.001$. At follow-up, 11 of the 30 participants met the remission criterion (HDRS score ≤ 7). Ten participants were still using antidepressants; two used benzodiazepines. In Table 1, characteristics of remitted and non-remitted MDD participants at

Table 1
Subject characteristics of depressed participants pre- and post-treatment.

	Pre-treatment	Post-treatment	
Variable	Depressed	Non-remitted at FU	Remitted at FU
n	30	19	11
Men	13	7	6
Women	17	12	5
Age in years	40	41	39
HDRS	24.2	15.1	3.2[a]
BDI	28.1	21.6	8[a]
Positive family history (%)	56	58	54
Previous episode(s) (%)	50	42	63

[a] Differences between remitted and non-remitted participants at follow-up: $P \leq 0.001$; [b]Differences between remitted and non-remitted participants at follow-up: $P \leq 0.05$.

follow-up are compared. Remitted MDD participants do not differ from non-remitted MDD participants in gender, age, positive family history of MDD and previous episode(s).

3.2. Daily stressors

Frequencies and appraisals of events and mean levels of stress in all groups (baseline MDD, remitted at follow-up, non-remitted at follow-up, and healthy controls) are presented in Table 2.

In total, 32 out of 180 (17.8%) negative events were considered to be internal negative events and therefore excluded from analyses. Frequencies, the appraised unpleasantness of negative events and level of social stress in non-remitted participants did not change from pre- to post-treatment (Table 2). The appraised importance and stressfulness of negative events and the mean level of activity stress decreased significantly in non-remitted participants from pre- to post-treatment. The experience of daily stressors in remitted participants was no longer significantly different from that of healthy controls, in terms of appraised stressfulness or importance of negative events or in levels of activity stress or social stress; however, remitted patients appraised negative events as more unpleasant, compared to controls (Table 2).

3.3. Momentary mood states after treatment

Mean PA in non-remitted participants was unchanged at follow-up compared to baseline (2.5 vs 2.1, $t\,(18) = -2.62$, $P = 0.09$). NA levels in non-remitted participants were also unchanged at follow-up compared to baseline (2.7 vs 3.1, $t\,(18) = 2.01$, $P = 0.06$). In remitted participants, mean PA remained significantly lower than in healthy controls (3.6 vs 4.5, $t\,(48) = 3.03$, $P = 0.004$), and mean NA was significantly higher (1.7 vs 1.3, $t\,(48) = 2.93$, $P = 0.005$). The level of residual depressive symptoms could explain these differences in mean NA and PA, as the post-treatment HDRS score was associated with higher mean NA ($r_s = 0.68$, $n = 11$, $P = 0.02$) and lower mean PA ($r_s = -0.63$, $n = 11$, $P = 0.04$) levels among remitted depressed participants.

Table 2
Comparison of frequencies (%) and appraisals (mean/SD) of reported negative events and mean ratings of social stress and activity stress.

Type of stress	Depressed at baseline (and non-remitted at FU) ($n = 19$)	Non-remitted at FU ($n = 19$)	Remitted at FU ($n = 11$)	Healthy ($n = 39$)
Negative events[a]	16%	12%	9%	16%
Unpleasant	5.9 (0.7)	5.6 (0.8)	5.5 (0.8)	4.7 (0.9)*
Important	5.1 (1.1)	3.9 (1.7)#	5.0 (1.4)	4.0 (1.2)
Stressful	5.8 (0.9)	5.2 (1.0)#	4.2 (0.9)	3.3 (1.2)
Activity stress	3.8 (0.5)	3.5 (0.7)#	2.9 (0.7)	2.5 (1.1)
Social stress	2.2 (1.1)	2.6 (1.4)	1.7 (0.5)	1.5 (1.3)

Note: frequencies and appraisals of negative events, levels of social stress and activity stress are compared between: MDD participants at baseline and non-remitted at 18-month follow-up and remitted versus healthy controls.
Differences between non-remitted participants at follow-up and depressed at baseline (paired *t*-test): #$P \leq 0.05$.
Differences between remitted participants at follow-up and healthy controls (*t*-test): *$P \leq 0.05$.
[a] Event frequencies are reported as percentages of the total number of valid ESM reports.

3.4. Stress reactivity at 18-month follow-up

Multilevel regression estimates of post-treatment stress reactivity to negative events (with associated appraisals), activity stress, and social stress are presented in Table 3.

Positive affect: the occurrence of negative events, social stress and activity stress were all associated with reductions in PA. Appraised unpleasantness, importance and stressfulness of negative events had no additional effects on PA. Further, the severity of depressive symptoms at follow-up (HDRS score) was not a significant predictor of the stress-related decrease in PA (all three stress types).

Negative affect: negative events, activity stress, and social stress were all accompanied by significant increases in NA. The increase in NA after negative events and activity stress was in both cases dependent on the severity of residual depressive symptoms at 18 months: higher HDRS scores were associated with higher increases in NA following stress. This was not the case for social stress, however: here, NA-reactivity was independent of the severity of depressive symptoms. Negative events that were appraised as more stressful were associated with further increases in NA; in contrast, appraised unpleasantness and importance of negative events had no effect on NA.

3.5. Stress reactivity in remitted and non-remitted depressed participants compared to healthy controls

Results of comparisons of stress responses at follow-up in remitted and non-remitted depressed patients with those in healthy controls (the reference group) are presented in Table 4.

Positive affect: the extent to which PA was lower in the context of negative events, activity stress, and social stress was similar in healthy controls, remitted, and non-remitted depressed participants.

Table 3
Multilevel estimates of the main effects of daily stress (negative event, activity, and social stress) at 18-month follow-up and the interaction effects of daily stress with Hamilton Depression Rating Scale (HDRS) on positive and negative mood states.

	PA	NA
Main effects		
Negative event	B = −0.301, $P = 0.001$	B = 0.522, $P < 0.001$
Unpleasantness	B = 0.022, $P = 0.678$	B = 0.023, $P = 0.577$
Importance	B = −0.022, $P = 0.480$	B = −0.027, $P = 0.260$
Stressfulness	B = −0.071, $P = 0.191$	B = 0.165, $P < 0.001$
Activity stress	B = −0.189, $P < 0.001$	B = 0.169, $P < 0.001$
Social stress	B = −0.112, $P < 0.001$	B = 0.162, $P < 0.001$
Interactions		
Negative event × HDRS	B < 0.001, $P = 0.976$	B = 0.020, $P = 0.029$
Activity stress × HDRS	B = 0.006, $P = 0.176$	B = 0.006, $P = 0.026$
Social stress × HDRS	B = 0.003, $P = 0.435$	B = −0.001, $P = 0.730$

B: unstandardized beta.

Table 4
Multilevel estimates of daily stress (negative event, activity, and social stress) × group (non-remitted and remitted MDD patients at follow-up and healthy controls) on positive and negative mood states (PA and NA).

Groups (with healthy controls as the reference group)	Type of stress	PA	NA
	Negative event		
Non-remitted		B = −0.106, P = 0.289	B = 0.255, P = 0.012
Remitted		B = −0.066, P = 0.589	B = 0.085, P = 0.501
	Activity stress		
Non-remitted		B = −0.010, P = 0.825	B = 0.087, P = 0.003
Remitted		B = −0.083, P = 0.126	B = 0.038, P = 0.283
	Social stress		
Non-remitted		B = 0.034, P = 0.387	B = 0.103, P = 0.005
Remitted		B = −0.059, P = 0.192	B = 0.117, P = 0.004

B: unstandardized beta. This table shows an interaction between daily stress (negative event, activity, and social stress) and group (non-remitted, remitted and healthy controls) with PA and NA as outcome measurements in order to examine whether the patient groups differ from healthy controls with respect to stress reactivity. Thus, non-remitted and remitted MDD patients were compared with healthy controls (the reference group).

Negative affect: non-remitted depressed participants showed significantly higher NA in relation to all three types of stress, compared to healthy controls. In contrast, remitted depressed participants did not differ from healthy controls in NA-reactivity to self-reported negative events and activity stress. In the case of social stress, remitted participants still reported significantly higher NA than healthy controls. Fig. 1 shows the levels of NA at different levels of social stress, stratified by group. The dose-response relationship between social stress and NA was more pronounced in the depressed groups. Differences in effect sizes between non-remitted and healthy controls were significant for average (B = 0.703, $P < 0.001$) and above average (B = 0.558, P = 0.017) appraisals of social stress. Remitted participants differed from healthy controls for average (B = 0.763, P = 0.001), above average (B = 0.677, P = 0.045) and strong appraisals of social stress (B = 0.645, P = 0.040).

4. Discussion

The current paper examined, with the use of ESM, differences in negative event frequency, appraisals, momentary mood states, and stress levels between healthy controls and remitted depressed participants after a naturalistic treatment period of 18 months. In addition, the follow-up results for non-remitted participants were compared with their own pre-treatment levels. Further, we tested the moderating role of residual depressive symptoms on stress reactivity to three types of stress (event-, activity-, and social stress). Last, we examined differences in stress reactivity between non-remitted, remitted, and healthy control groups.

Results showed that participants with non-remitted compared to remitted depression appraised negative events as more stressful. NA was higher in the context of recent negative events and activity-stress, dependent on the severity of current depressive symptoms. Of note, relatively high NA in relation to social stress at follow-up was independent of the severity of depressive symptoms. In comparison with healthy controls, remitted depressed participants continued to show a heightened sensitivity to social stress only, whereas non-remitted depressed participants showed greater NA-reactivity in relation to all three types of stress.

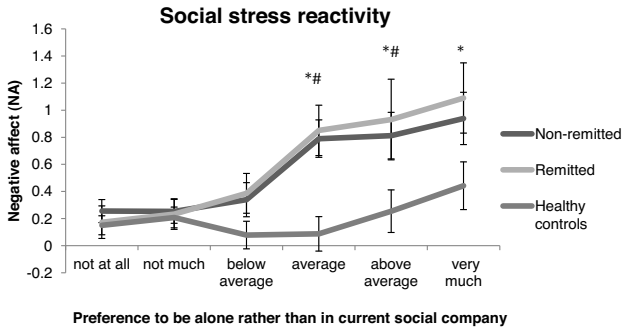

Fig. 1. Comparison of social stress reactivity in healthy controls, non-remitted, and remitted MDD patients, with NA as outcome measurement. *Significant differences (*$P \leq 0.05$) in effect sizes for very unpleasant appraisals of company (effect of social stress on negative affect) between remitted and healthy controls. #Significant differences (#$P \leq 0.05$) in effect sizes for very unpleasant appraisals of company (effect of social stress on negative affect) between non-remitted and healthy controls.

4.1. Changes and differences in event frequencies, stress appraisals and mood states

In many respects, remitted participants could not be distinguished from healthy controls: their stress levels and event frequencies appear to have normalized. However, participants with remitted depression still showed significantly lower mean PA and higher mean NA levels compared to healthy, never-depressed individuals. This may serve as support for recent work showing that clinical remission based on current cut-off scores does not imply restoration of pre-morbid functional capacities in different life domains [47].

Non-remitted depressed participants demonstrated some significant changes in negative event frequencies, stress levels and mean NA/PA levels in comparison with their own baseline levels. These event frequencies are in line with the baseline event frequencies reported in an earlier study in this sample [32].

4.2. Moderating effect of residual symptoms on stress reactivity

Until now, virtually no data were available on changes in stress reactivity in depressed individuals post-treatment. As we had expected, all three types of daily stress (event-, activity-, and social stress) were associated with lower PA and higher NA, compared to non-stress contexts. Furthermore, the increase in NA after event- and activity-stress was dependent upon the severity of residual depressive symptoms. The moderating effect of severity of depressive symptoms on NA-reactivity to event- and activity-related stress suggests that the increased NA-reactivity to these types of stress is state-dependent. This is in line with a study that showed that NA-reactivity to activity stress decreased only in clinically improved participants after six weeks of treatment with imipramine or placebo [44]. A novel finding was that the increase in NA after social stress was independent of the severity of persistent depressive symptoms. This may be indicative of a pre-morbid and/or acquired sensitivity to social stress in subjects with MDD, which is not related to the level of current symptomatology.

4.3. Stress reactivity compared to healthy controls

4.3.1. Event- and activity stress

The increased NA-reactivity to activity-related stress in non-remitted depressed participants was significant higher than in healthy never depressed individuals. This finding is in concordance with the study of Wichers et al. (2009). Taken together, these

results show that increased NA-reactivity to activity stress appears a stable phenotype when an episode of MDD becomes chronic.

Concerning the stronger event-related stress reactivity in non-remitted depressed participants in comparison with healthy controls, it should be noted that the impact of stress on NA actually depends upon the appraised stressfulness of the event. Previous ESM reports also reported this mediating role of the level of stressfulness of an event on mood reactivity [10,32]. Although Bylsma et al. [10] and Peeters et al. [32] reported respectively a normal or blunted stress reactivity in depressed patients compared to healthy controls, they also examined the relationship between the appraised stressfulness and stress reactivity to negative events. They both found greater increases in NA as subjective appraisals of stressfulness increased in depressed patients. Peeters et al. (2003) concluded that their results can be interpreted as "evidence for environmental hypersensitivity (event appraisals) and on the other hand (mood changes), they may be construed as evidence for hyposensitivity" [32].

4.3.2. Social stress

Remitted depressed participants remained more sensitive to experiences of social stress than healthy controls, although event- and activity-related stress reactivity normalized. This finding cannot be explained by the presence of residual symptoms, as social stress related increases of NA were independent of severity of depressive symptoms. There exist several explanations for these findings. First, this increased sensitivity may be perceived as indicative of a "scar" in stress reactivity as a result of the experience of an episode of MDD [45,24,5]. However, a scarring effect seems less likely because one would expect such effect on all three types of stress reactivity that we examined and not only on social stress. Unfortunately no pre-morbid data from our participants are available to test this hypothesis. An alternative possibility to investigate this hypothesis would be to examine whether social stress reactivity increases as a function of more depressed episodes. Unfortunately, our sample size is underpowered for such analysis. Second, it has also been suggested that increased NA-reactivity to social stress puts people at risk for developing MDD or recurrence [4,13,43,30]. As such, increased social stress reactivity may be conceived as a proxy for other risk factors that are known to play a role in the development of MDD such as neuroticism [28,2,25] and increased self-esteem liability [8,35,34,11]. Further, in favour of a pre-morbid vulnerability, there is emerging evidence that increased NA-reactivity to social stress is indicative of a genetic predisposition to respond with more NA to small social stressors and may function as an intermediate endophenotype of MDD [43,42,29,27]. More specifically, specific variations of the *BDNF* gene, Met carriers of the BDNF ^{Val66Met} genotype, are associated with a higher NA-reactivity to social stress [43,42]. This is in line with evidence that sensitivity to perceived social stress is an important vulnerability factor in teenagers that develop depression at a later stage [39].

Our current paper supports the notion that daily life increased NA-reactivity to social stress is an important endophenotype in the course of MDD, which may increase risk for the development and recurrence of a depressive episode. Future research should contribute to a better understanding of the specific role of social stress reactivity in daily life in the risk for and relapse in MDD.

4.3.3. Discrepancies between findings from experimental and daily life studies

Stress reactivity in experimental studies is mainly induced with the use of films, pictures or emotional imagery. Grillon et al. [21] argued that the threat in these procedures is typically mild, hypothetical and/or may lack personal relevance. Other authors have also pointed to the fact that stressors may be experienced differently by each subject, depending on the meaning the situation has for this particular individual [6,37]. This might explain why some daily life studies found increased stress reactivity instead of blunted stress reactivity. It may be suggested that blunted stress reactivity in case of hypothetical and non-personal threats and increased stress reactivity in case of personal relevant threats coexist in MDD [21].

4.4. Strengths and limitations

Our study has several strengths. To our knowledge this is the first study to examine stress reactivity to various minor daily stressors before and after a naturalistic MDD treatment. Secondly, because our study was based on a substantial follow-up period (18 months), we were able to examine stress reactivity in participants who were in a period of stable remission compared to those with more chronic depression. This is of particular importance because it was unclear whether clinical improvement was accompanied by normalization of daily stress reactivity.

Some limitations also apply. Although the multiple measurements derived from the ESM and modelled with multilevel regression techniques afforded sufficient statistical power to detect differences in daily life stress reactivity, our relatively small sample size warrants replication in larger samples. Next, due to the small number of remitted participants we were not able to test pre-to-post individual differences in stress reactivity. Further, we did not use a structured interview (SCID-I) at follow-up, but instead relied on a cut-off score of 7 on the 17-item HDRS to define remission from MDD, as recommended in literature. Therefore, it is uncertain if our results apply to subjects whose remission status is assessed with a formal diagnostic interview. Further, the fact that, in addition to psychotherapy, all participants underwent antidepressant treatment according to current practice guidelines (APA, [1] means that antidepressants may have influenced ESM stress-reactivity measurements). An earlier ESM study showed that treatment with antidepressants, in comparison to placebo, significantly decreased NA-reactivity to activity stress after six weeks [44]. Also, even with a time-sampling approach like ESM, retrospective biases cannot be entirely eliminated, given that participants reported negative events over 90 min intervals. Furthermore, causal associations between events and mood states cannot be conclusively determined, because event and affect reports were collected simultaneously. However, in support of our assumption that events most likely influenced emotions (and not vice versa), we previously reported that prior events at baseline in the same sample, controlling for effects of current events, were associated with persistent changes in PA and NA [32]. Further, no reliability data on diagnoses with the use of SCID interview are available. A research psychiatrist (FP) assessed all SCID interviews. No other raters were involved.

Last, NA and PA were rated at the same moment that activity and social stress were assessed. This is in contrast with the assessment of small negative events, which may have occurred maximally 90 minutes before mood assessment. As a result of this delay, we cannot rule out an underestimation of the association between negative events and mood in comparison to mood responses associated with the two other types of stress. In conclusion, the current findings suggest that greater stress reactivity to negative events and stressful daily activities may be a state-dependent characteristic of MDD, normalizing upon remission. Heightened stress reactivity to social contexts, on the other hand, was observed in remitted as well as in non-remitted patient groups, suggesting that sensitivity to social stress may reflect an underlying vulnerability for development and recurrence of MDD.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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